#7 Decl. attached 8/14/02

Express Mail No.: EL 477 037 820 US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Spear *et al.* Confirmation No.: 3399

Application No.: 09/924,231 Group Art Unit: 1648

Filed: August 8, 2001 Examiner: Wortman, D.

For: PHARMACEUTICAL COMPOSITIONS COMPRISING HERPES VIRUS ENTRY RECEPTOR PROTEIN Attorney Docket No.: 7853-239

DECLARATION OF ABBIE CELNIKER UNDER 37 C.F.R. § 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Abbie Celniker do declare and state:

1. I presently hold the position of Vice President of Biotherapeutics at Millennium Pharmaceuticals, Inc. Millennium Pharmaceuticals, Inc. is the exclusive licensee of the above-identified application ("the '231 application"). My academic and technical experience and honors, and a list of my publications are set forth in my *curriculum vitae*, attached as Exhibit 1.

2. I have read and am familiar with the following materials:

   a. the '231 application;

   b. the claims currently pending in the '231 application;

   c. the Office Action, dated March 5, 2002, issued in connection with the '231 application; and

   d. Exhibits 2-9 discussed below.

3. The invention claimed in the '231 application is directed to pharmaceutical compositions comprising Herpes Virus Entry Mediator ("HVEM") protein. HVEM is also

known in the art as TR2 (TNF Receptor-, or TNFR-, related 2), ATAR (another TRAF (TNF Receptor Associated Factor)-associated receptor), and HveA (herpesvirus entry protein A).

4. HVEM is a member of the family of receptors designated the tumor necrosis factor receptor/nerve growth factor receptor (TNFR/NGFR) family ('231 specification at page 1, last paragraph). HVEM was identified by the present inventors on the basis of its ability to confer susceptibility to herpes simplex virus type 1 ("HSV1") upon Chinese Hamster Ovary ("CHO") cells ('231 specification at pages 10-12). Briefly, as described by the specification, CHO cells that do not express HVEM are resistant to HSV1 entry, as evidenced by lack of expression of β-galactosidase, a reporter gene carried by the virus employed in the studies described in the '231 specification, following contacting the cells with the virus. In contrast, CHO cells that recombinantly express HVEM are sensitive to HSV1 infection, which is evidenced by their expression of the viral reporter β-galactosidase.

5. The references attached hereto as Exhibits 3-6, published before what I understand is the filing date of the first parent application of the '231 application and discussed in more detail in ¶¶ 6-9 below, corroborate that one of ordinary skill in the art would recognize that a dominant negative receptor of the TNF receptor family, such as a soluble receptor, interferes with binding of a TNF-class ligand to its receptor. These references further corroborate that one of ordinary skill in art would recognize that, where a TNF-class ligand mediates entry of a pathogen into a host cell, such as a human cell, via a TNF receptor family member, a soluble form of the receptor would interfere binding of the ligand to the host cells, and therefore inhibit entry of the pathogen into the host cell. Accordingly, one of ordinary skill in the art would recognize that a dominant negative form of HVEM, such as soluble HVEM, of which the native form (*i.e.*, cellular membrane-bound form) was shown by the inventors to mediate entry of herpes virus into mammalian cells, would be useful in inhibiting herpes virus entry into mammalian cells. Thus, one of ordinary skill in the art at the time the earliest parent of the '231 application was filed would recognize that an exogenous HVEM molecule which sequesters herpes virus from binding to cellular HVEM and thus interferes with the ability of herpes virus to infect cells could be formulated into a pharmaceutical composition for therapeutic or prophylactic use against herpes virus.

For these reasons and the reasons discussed in ¶¶6-16 below, one of skill in the art would recognize that dominant exogenous HVEM molecules, such as soluble HVEM, can be used to treat or prevent infections by HSV. Further, one of skill in the art, using the teachings of the specification and routine methodology, would be able to make and administer pharmaceutical compositions comprising such HVEM molecules. In particular, pharmaceutical formulations are taught in the specification of the '231 application, for example in Section V at pages 24-25, and are also well known in the art (see, for example, Remington's Pharmaceutical Sciences, Alfonso R. Gennaro ed., Mack Publishing Co. Easton, Pa., 19th ed., 1995, pp. 1495-1560, attached hereto as Exhibit 2). Methods of administration are also both taught in the specification (second paragraph on page 25) and well known to the skilled artisan.

ADMINSITRATION OF HVEM IS EXPECTED TO INHIBIT INFECTION BY OR SPREADING OF HERPES VIRUS

6. Gray *et al.* ("Gray"), Exhibit 3 attached hereto, establishes that a soluble receptor of the TNF receptor family inhibits the biological activity of its ligand. Gray demonstrates that conditioned medium from COS cells transfected with the extracellular domain of the TNF receptor both inhibited the binding of TNFα to cells which express the endogenous, *i.e.*, membrane-bound, receptor by approximately 70% (Fig. 4A at page 7383) and inhibited a biological activity of TNFα, induction of cytolysis of WEHI cells, by about 60% (Fig. 4B at page 7383).

7. Ashkenazi *et al.*, Exhibit 4 attached hereto ("Ashkenazi"), demonstrates that a soluble form of a TNF receptor, namely a fusion protein of the extracellular domain of human type 1 TNF receptor and an immunoglobulin ("TNFR-IgG"), inhibits both *in vivo* as well as *in vitro* biological activity of TNF. *In vitro*, TNFR-Ig was able to block TNF-induced lysis of actinomycin-treated murine cells (Fig. 3 at page 10537). Further, *in vivo*, administration of TNFR-Ig to experimental mice was able to protect the mice against TNF-mediated toxic shock induced by *Salmonella*-derived endotoxin (Fig. 4 at page 10538). Accordingly, Ashkenazi establishes that administration of a soluble form of a TNF class of receptor to a mammal inhibits the biological activity of the endogenous receptor.

8. Ward *et al.*, Exhibit 5 attached hereto ("Ward"), describes using a soluble form of CD4, the human immunodeficiency virus ("HIV") entry receptor, comprising two extracellular immunoglobulin domains of CD4 and a human immunoglobulin, referred to hereinafter as CD4-Ig, to block HIV-1 infection in chimpanzees. A comparison was made of the course of HIV infection in chimpanzees treated with CD4-Ig (Animals 37 and 43) prior to and following challenging the animals with HIV versus a control animal that received the HIV challenge but no CD4-Ig treatment (Animal 62). Although the control chimpanzee, Animal 62, showed signs of HIV infection as early as three weeks following the HIV challenge, the two chimpanzees that received the CD4-Ig regimen were HIV negative by three different assays at the end of the 47-week testing period (Table 1 at page 435).

9. Greve *et al.*, attached hereto as Exhibit 6 ("Greve"), describes experiments in which the effect of two soluble forms of intercellular adhesion molecule-1 ("ICAM-1"), the receptor of the majority of human rhinoviruses, on the binding of human rhinovirus type 3 (HRV3) to full length ICAM-1 and HRV3 infectivity. One of the soluble forms of ICAM-1 tested in this study corresponded to the entire extracellular domain of ICAM-1, and the other to ICAM-1's two N-terminal immunoglobulin-like domains, referred to hereinafter as tICAM(453) and tICAM(185), respectively. In an *in vitro* binding assay, both soluble forms of ICAM-1 were capable of inhibiting the binding of radiolabeled HRV3 to ICAM-1 immobilized on a microtiter dish (Fig. 3A at page 6018). tICAM(453) and tICAM(185) were also capable of inhibiting HRV3 infection of HeLa cells (Fig. 3B at page 6018), and further inhibited HRV3 replication in HRV3- infected HeLa cells (Fig. 3B at page 6018).

10. I conclude, based on the references described in ¶¶ 6-9 above and the data described in the '231 specification, that recombinant HVEM would bind to and sequester HSV1 particles, thereby preventing their binding to cellular HVEM or any other cellular receptor, thus preventing HSV1 infection of cells or the spread of HSV1 from cell to cell following infection.

SOLUBLE HVEM IS EXPECTED TO BE USEFUL IN TREATING OR PREVENTING HSV INFECTIONS

11. Wild-type HSV-1 can use HVEM for cellular entry, as transfection of CHO cells with HVEM renders them susceptible to HSV-1 ('231 specification, page 13 at second paragraph). Viral entry through HVEM is thought to be at least in part mediated by HSV viral envelope glycoprotein D, or gD ('231 specification, page 13 at third paragraph).

12. A phenomenon called gD-interference has been observed for herpes viruses. Briefly, gD interference refers to cellular resistance to herpesvirus infections in cells in which wild-type gD is expressed. The inventors of the '231 application observed gD interference of HSV1 infections in gD- and HVEM-expressing CHO cells, even when the gD was of HSV2 origin ('231 specification at pages 13-14). Because gD interference is thought to occur by gD sequestration of a cellular receptor, the gD interference observed by the inventors suggests that HVEM interacts with gD of both HSV1 and HSV2. This is consistent with the hypothesis that gD interference results from competition between cell-associated gD and virion-associated gD for a common target, *i.e.*, HVEM. This observation has been verified (see, *e.g.*, Montgomery *et al.*, Exhibit 7 attached hereto, and Whitbeck *et al.*, 1997, Exhibit 8 attached hereto).

13. Although HVEM can mediate cellular entry of HSV1 and HSV2 in CHO cells, HVEM-expressing CHO cells remain resistant to certain mutant strains of HSV1 ('231 specification, page 13 at third paragraph), suggesting the presence of other receptors. Indeed, other receptors for herpesviruses have been identified following the effective filing date of the '231 application (*see*, *e.g.*, background section of Whitbeck *et al.*, 1999, Exhibit 9 attached hereto).

14. However, despite the existence of more than one cellular herpesvirus receptor, evidence suggests that one particular region of herpesvirus gD protein is responsible for binding to a number of these receptors (*see*, *e.g.*, Whitbeck *et al.*, Exhibit 9, in particular Fig. 11 at page 9888).

15. Because herpesvirus gD protein is capable of binding more than one cellular receptor through a common domain, one of skill in the art would conclude that obstruction of

this region in gD would inhibit gD from binding to its cellular receptors and therefore inhibit viral infection of cells, in a manner analogous to gD interference among various strains of HSV. This is consistent with the observation that the region of gD responsible for binding to HVEM and another cellular receptor, HveC, overlaps a region of gD that is recognized by a particular class of herpesvirus neutralizing antibodies (*see, e.g.*, Whitbeck *et al.*, Exhibit 9, in particular Fig. 11 at page 9888).

16. In view of the above observations, one of skill in the art would expect that soluble HVEM, given its ability to bind to gD of wild type HSV1 and HSV2, would be useful in preventing the binding of HSV1 and HSV2 to a cellular receptor, thereby inhibiting infection and spreading of these viruses in mammalian cells.

17. In summary, the teaching presented in the '231 application, coupled with the state of the art at the time the first parent of the '231 application was filed, would allow one of skill in the art to routinely make and use pharmaceutical compositions comprising soluble HVEM protein. One of skill in the art would expect administration of such compositions to be useful in achieving clinically beneficial results in the treatment or prevention of infections by wild type HSV1 and HSV2.

18. I declare further that all statements made in this Declaration of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: _____ _____

Abbie Celniker

Attachments:

Exhibit 1: *Curriculum Vitae* of Abbie Celniker.

Exhibit 2: Remington's Pharmaceutical Sciences, Alfonso R. Gennaro ed., Mack Publishing Co. Easton, Pa., 19th ed., 1995, pp. 1495 to 1560.

Exhibit 3: Gray *et al.*, 1990, "Cloning of human tumor necrosis factor (TNF) receptor cDNA and expression of recombinant soluble TNF-binding protein," Proc. Nat'l Acad. Sci. U.S.A. 87:7380-7384.

Exhibit 4: Ashkenazi *et al.*, 1991, "Protection against endotoxic shock by a tumor necrosis factor receptor immunoadhesin," Proc Natl Acad Sci U.S.A. 88(23):10535-39.

Exhibit 5: Ward *et al.*, 1991, "Prevention of HIV-1 IIIB Infection in Chimpanzees by CD4 Immunoadhesin," Nature 352:434-436.

Exhibit 6: Greve *et al.*, 1991, "Mechanisms of Receptor-Mediated Rhinovirus Neutralization Defined by Two Soluble Forms of ICAM-1," Journal of Virology 65(11):6015-6023.

Exhibit 7: Montgomery *et al.*, 1996, "Herpes simplex virus-1 entry into cells mediated by a novel member of the TNF/NGF receptor family," Cell 87:427-436.

Exhibit 8: Whitbeck *et al.*, 1997, "Glycoprotein D of herpes simplex virus (HSV) binds directly to HVEM, a member of the tumor necrosis factor receptor superfamily and a mediator of HSV entry," J. Virol. 71(8):6083-93.

Exhibit 9: Whitbeck *et al.*, 1999, "The major neutralizing antigenic site on herpes simplex virus glycoprotein D overlaps a receptor-binding domain," J. Virol. 73(12):9879-90.

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Education:

1986, Ph.D., Molecular Biology, University of Arizona. Immunological Studies of Human Cathepsin D

1980, B.A., Biology, University of California, San Diego

Experience Overview:

- Extensive experience in the area of recombinant protein pharmaceutical development and commercialization including; functional area oversight, regulatory submissions, interactions with CEBR and CDER, and project team leadership and participation.

- Scientific expertise in the areas of transplantation biology, co-stimulation, growth and wasting.

- Technical expertise in the areas of; monoclonal antibody development and characterization, immunoassay and analytical methods development and Preclinical biology.

- Managerial experience including the management of individuals and groups consisting of Ph.D., DVM, Post-doctoral and research associate level positions.

- Compliance experience including the organization and maintenance of GLP and GMP compliant laboratories and information management systems.

- Translational biology experience focused on the integration of novel analytical methods into clinical studies and the movement of therapeutic proteins from research into the clinic.

Employment:

June 2000 to Present, Vice President, Biotherapeutics, Millennium Pharmaceuticals, Cambridge, MA. Responsibilities include:

- Oversight of the following functional areas: Therapeutic Antibody Technology Group, Protein Sciences (discovery and process development), Biological Assay Development, Mouse Models Development and the Animal Resources Group.

- Participation on the Discovery Scientific Review Committee, Development Scientific Review Committee and Product Team (development portfolio management)

October 1999 to June 2000, Assistant Vice President, Predevelopment – Biopharmaceutical Core Technologies, **Genetics Institute of Wyeth Ayerst Research**, Andover/Cambridge, MA. Responsibilities included:

- Oversight of the following functional areas: Therapeutic Antibody Technology Group, Research Protein Supply, Proteomics, Bioanalytical Sciences, Pharmacokinetic and Pharmacodynamic Sciences, Laboratory Animal Resources, Preclinical Scientific Communications, Research Operations and the External Research Department.

- Oversight of "predevelopment process" for therapeutic proteins moving from discovery research into development (Lead Candidate through IND).

- Preclinical Project Team Leader for the Anti-B7.1/Anti-B7.2 Program in GvHD and Renal Transplantation

November 1993 to June 1999, Director /Senior Scientist of Bioanalytical Sciences at **Genetics Institute**, Andover, MA. Responsibilities included:

- Oversight of the Antibody Technology Group, Bioanalytical Sciences and the Preclinical Transcriptional Profiling group (Gene Expression Monitoring).

- The establishment and oversight of a GLP compliant immunoassay lab, including laboratory automation (sample tracking, sample manipulation and data transfer), assay validation and facility management.

- Member of the Analytical Coordinating Group (ACG) responsible for the immunoassays used for identity testing, ligand binding analysis and immunoassays for host cell protein impurities to support process and product development.

- Oversight of the assessment and interpretation of anti-product immune responses for Preclinical and clinical studies.

- Preclinical Project Team Leader for the Anti-B7.1/Anti-B7.2 Program in GvHD and Renal Transplantation

May of 1993 to November 1993, Associate Director/Senior Scientist, Medicinal and Analytical Chemistry, **Genetech Inc.**, South San Francisco, CA. Responsibilities included:

- Oversight of the Bioanalytical Methods Development group, responsible for immunoassay development for research, Preclinical, clinical and product development support

- Preclinical Research Project Team Leader for the IGF-1 Program

June 1986 to May of 1993, Scientist, Medicinal and Analytical Chemistry, **Genentech Inc.**, South San Francisco, CA. Responsibilities included:

- Development of antibodies and immunoassays for the quantitation of human and animal growth hormones in serum and urine and the assessment of the anti-growth hormone antibody response.

- Development of antibodies and immunoassays for the quantitation of human Insulin-like Growth Factor 1 (IGF-1) and IGF-1 binding proteins in serum and urine to support preclinical and clinical pharmcokinetics and pharmacodynamics

- Development of antibodies and immunoassays for the quantitation of gamma interferon, TNF-alpha, HSA, Human Relaxin, Pro-Relaxin, and Relaxin "A" and "B" chains in serum, urine and cell expression systems

- Development of immunoassays for the quantitation of E. coli and CHO derived host cell protein impurities

1984 to 1986, Research Associate, **University of Arizona Cancer Center**, Veteran's Administration Hospital, Tucson, AZ. Responsibilities included:

- Establishment of primary cells lines from prostate tumor and benign prostatic hypertrophy specimens.

- Development of assays to differentiate cytostatic from cytotoxic biological response modifiers.

- Development of immunohistochemical staining methods for the detection of prostate cancer cells in bone marrow.

Publications:

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